

FINAL TECHNICAL REPORT

"IMMUNOTOXICOLOGY OF JP-8 JET FUEL"

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November 2000

David T. Harris, Ph.D.
Dept. of Microbiology & Immunology
Bldg. 90-Main Campus
University of Arizona
Tucson, AZ 85721
Tel:(520)626-5127
FAX:(520)621-6703
Email:davidh@U.Arizona.EDU

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13. ABSTRACT (Maximum 200 words) Chronic jet fuel exposure could be detrimental to Air Force personnel, not only by adversely affecting their work performance but also by predisposing these individuals to increased incidences of infectious disease and cancer. Chronic exposure to jet fuel has been shown to adversely affect human liver function, to cause emotional dysfunction, to cause abnormal electroencephalograms, to cause shortened attention spans, and to decrease sensorimotor speed. Currently, there are no standards for personnel exposure to jet fuels of any kind, let alone JP-8 jet fuel. Kerosene based petroleum distillates have been associated with hepatic, renal, neurologic and pulmonary toxicity in animals models and human occupational exposures. The U.S. Department of Labor, Bureau of Labor Statistics estimates that over 1.3 million workers were exposed to jet fuels in 1992. Thus, jet fuel exposure may not only have serious consequences for USAF personnel, but also may have potential harmful effects upon a significant number of civilian workers. Short-term (7 day) JP-8 jet fuel exposure causes lung injury as evidenced by increased pulmonary resistance, a decrease in bronchoalveolar lavage concentrations of substance P, increased wet lung/body weight ratio, and increased alveolar permeability. Long-term exposures, although demonstrating evidence of lung recovery, results in injury to secondary organs such as liver, kidneys and spleen.					
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ABSTRACT

Chronic jet fuel exposure could be detrimental to Air Force personnel, not only by adversely affecting their work performance but also by predisposing these individuals to increased incidences of infectious disease and cancer. Chronic exposure to jet fuel has been shown to adversely affect human liver function, to cause emotional dysfunction, to cause abnormal electroencephalograms, to cause shortened attention spans, and to decrease sensorimotor speed. Currently, there are no standards for personnel exposure to jet fuels of any kind, let alone JP-8 jet fuel. Kerosene based petroleum distillates have been associated with hepatic, renal, neurologic and pulmonary toxicity in animals models and human occupational exposures. The U.S. Department of Labor, Bureau of Labor Statistics estimates that over 1.3 million workers were exposed to jet fuels in 1992. Thus, jet fuel exposure may not only have serious consequences for USAF personnel, but also may have potential harmful effects upon a significant number of civilian workers. Short-term (7 day) JP-8 jet fuel exposure causes lung injury as evidenced by increased pulmonary resistance, a decrease in bronchoalveolar lavage concentrations of substance P, increased wet lung/body weight ratio, and increased alveolar permeability. Long-term exposures, although demonstrating evidence of lung recovery, results in injury to secondary organs such as liver, kidneys and spleen.

We have observed that short-term (7 days) exposure of C57BL6 mice to low concentrations ($100-500 \text{ mg/m}^3$) of JP-8 jet fuel results in profound and significant alterations on the immune system. Organ weights (spleen and thymus) and total cell numbers recovered from each of the major immune system organs (spleen, thymus, lymph nodes, bone marrow and peripheral blood) were significantly reduced. Flow cytometric analyses revealed that T cell populations were lost with significant increases in inflammatory and B cell populations in these organs. JP-8 exposure resulted in a significant depression of immune function (as measured by proliferative assays) of the residual cells which could not be overcome by the addition of exogenous immune response modifiers, and which may be indicative of a generalized inflammatory response. Mice exposed to a 7 day JP-8 jet fuel exposure exhibited an ability to recover from the immune alterations observed. Although immune organ weights recovered to normal levels within a week of cessation of exposure, up to one month was required to return immune organ cell numbers to baseline levels in the spleen and thymus. Cell numbers in the bone marrow, lymph nodes and peripheral blood recovered more quickly. Significantly, recovery of immune function was more profoundly affected, taking more than one month to recover to normal levels. Thus, short-term, low concentration exposures to JP-8 jet fuel resulted in long lasting immune alterations. Further, JP-8 exposure resulted in a loss of natural killer (NK) cell function, lymphokine activated killer (LAK) cell activity, and cytotoxic T lymphocyte (CTL) capacity. Additional analyses demonstrated that precursor cells for both cytotoxic and helper T cells had been affected by the exposures. Further, the detrimental effects of JP-8 exposure on the immune system are evidenced after only a few days of (1 hour/day) exposure. That is, one does not have to wait for 7 days of exposure to observe significant changes in the immune system. Experiments have elucidated the minimal exposure period to detect such changes in immune organs and immune function. These experiments revealed that the effects on the immune system could be observed with as little as 1 hour of JP-8 exposure. The damage to the immune system occurred rapidly and was cumulative in nature. Work has recently been completed demonstrating that JP-8

exposure rapidly induces significant levels of IL-10 and prostaglandin E2 secretion into the blood, which may help to explain the JP-8-induced immune dysfunction. We have also found that these immune effects were not restricted to JP-8 exposures but also could be found in animals exposed to JP8+100 and to Jet A1. These findings seem to indicate that it is the exposure to the jet fuel hydrocarbons itself that is toxic for the immune system, rather than exposure to any of the fuel additives. Finally, we have been collaborating extensively with Dr. Frank Witzmann (IUPUI), another AFOSR-funded investigator, to examine cellular changes induced by jet fuel exposure by proteomic mapping.

Interestingly, treatment of the mice with the neuropeptide substance P (1 uM, 15 minutes) immediately after JP-8 exposure was able to reverse many of the observed effects. That is, substance P administration was able to protect/reverse the effects of JP-8 jet fuel exposure on immune organ weights, immune organ numbers, and immune function. Confirmation of the role of substance P in this process was found in that administration of substance P inhibitors generally made the effects of JP-8 exposure even worse. We have now completed our studies of the mechanisms of substance P protection of the immune system from jet fuel exposure. We found that SP could be administered both prior to as well as after JP-8 exposure, but the time-frame for such treatments were quite limited. Studies are currently in progress to identify the active components/metabolites of substance P responsible for the protective effects.

Thus, exposure of individuals to JP-8 jet fuel induces significant immune dysfunction that may result in increased risk of infectious disease and cancer. However, it may be possible to reverse or prevent many of these effects through the administration of a common neuropeptide. It is absolutely critical to ascertain and understand the potential consequences of immune function alterations as it pertains to the short-term and long-term health and well-being of exposed personnel. The results obtained in these studies should have significant implications for the health, well-being and medical treatment of JP-8 exposed individuals.

Interestingly, treatment of the mice with the neuropeptide substance P (1 uM, 15 minutes) immediately after JP-8 exposure was able to reverse many of the observed effects. That is, substance P administration was able to protect/reverse the effects of JP-8 jet fuel exposure on immune organ weights, immune organ numbers, and immune function. Confirmation of the role of substance P in this process was found in that administration of substance P inhibitors generally made the effects of JP-8 exposure even worse.

Two recent studies have also provided some interesting preliminary data. In the first study, exposure of mice to JP-8+100 jet fuel (1000 mg/m³) also induced immunotoxicological damage comparable to that observed with JP-8 jet fuel alone. In the second study, injection of mice with substance P 15 minutes prior to JP-8 exposure was as effective in preventing the immunotoxicological effects of JP-8 jet fuel as administering substance P after the JP-8 exposure period. Studies are currently underway to identify the active components/metabolites of substance P responsible for the protective effects.

Thus, exposure of individuals to JP-8 jet fuel may result in increased risk of infectious disease, cancer and autoimmune disease. However, it may be possible to reverse or prevent many of these effects through the administration of a common neuropeptide. It is absolutely critical to ascertain and understand the potential consequences of immune function alterations as it pertains to the short-term and long-term health and well-being of exposed personnel. The results obtained in these studies should have significant implications for the health, well-being and medical treatment of JP-8 exposed individuals.

OBJECTIVES/STATEMENT OF WORK:

The Specific Aims of the grant for Year 03 were as follows.

EXPERIMENTS PLANNED FOR YEAR 03.

1. Effect of JP-8 Exposure on the Rat Immune System.

After consultation with the AFOSR it was decided to delay this particular specific aim of the project. It was felt that at this time there was sufficient data available from different animal species to identify JP-8 jet fuel as a significant toxicological agent.

2. Effect of De-Icer Administration on the Immune System.

After consultation with the AFOSR this particular topic of the project was eliminated to pursue the other topics discussed above.

3. Effect of JP-8 Exposure on the Human Immune System.

During the third year of the grant we have only just initiated this specific aim. This work is to be performed in collaboration with Dr. Terrence Risby (Johns Hopkins University). However, Dr. Risby has just now begun this work, and it is our understanding that the site of this work has been changed (from Dover Air Force Base to Montana National Guard Air Base) and will hopefully begin during the final months of year 03 of the project, and will be continued if the grant application is renewed.

As the above portions of the project were delayed or changed, the other work described above was initiated and completed after consultation with the AFOSR.

4. Completion of Proteomics Study with F. Witzmann.

This portion of the project has been successfully completed. We have sent Dr. Witzmann immune organs and tissues (thymus, spleen, blood, bone marrow and lymph nodes) from animals exposed to varying concentrations of JP-8 jet fuel (250-2500 mg/m³) for varying periods of time (1 h/d for 1 to 7 days, and 2-4 h/d for 1 to 4 days). Dr. Witzmann is in the process of analyzing the data obtained from these experiments (see Dr. Witzmann's progress report for details). If necessary, we will also send Dr. Witzmann isolated, specific lymphocyte subpopulations from the organs of exposed animals for his analyses.

5. Completion of IL-10 Measurements Study.

This portion of the project has been successfully completed. Furthermore, we were also able to obtain measurements of prostaglandin E2 levels from exposed animals. Please see above for details. A manuscript is now in preparation.

6. Analysis of JP-8 Exposures in Humans in Cold Weather Locations (Alaska)

This project will be conducted in collaboration with Dr. Mark Witten and with the Navy. This project was initially delayed due to funding delays from the AFOSR. However, monies have now been obtained and this project will be performed in November 2000 in Anchorage, Alaska.

7. Completion of Analysis of the Effects of Substance P on JP-8-Induced Immunotoxicity.

This project has been completed and a manuscript submitted for publication. The parameters of SP administration to effect protection from and/or reversal of JP-8 effects on the immune system has been determined.

8. Analysis of Jet Fuel Source on Immunotoxicity.

This project has been completed and a manuscript submitted for publication. We have found that JP-8, JP-8+100 and Jet A1 all induce similar immunotoxicity in exposed individuals. These findings indicate that both military and civilian workers may be at similar occupational risk in terms of their health effects.

9. Kinetics of JP-8-Induced Immunotoxicity.

This project has been completed and a manuscript submitted for publication. We have found that the detrimental effects of JP-8 exposure on the immune system begin immediately upon exposure and are cumulative over the course of the exposure period. Thus, there appears to be no safe exposure period for exposed workers.

STATUS OF EFFORT:

We have continued our investigation of the immunotoxicological effects of exposure to JP-8 jet fuel, making use of murine animal models. Our experiments have revealed that the immune system may be one of the most sensitive indicators of toxicological effects in the exposed individual. Short-term, low-concentration JP-8 exposure resulted in a profound and significant alterations in many immune parameters measured (immune organ weights, immune cell numbers, mitogenic responses, CTL, NK and LAK effector cell mechanisms, and helper and cytotoxic T

cell precursors) that occur as early as two days after exposure. We also have defined the parameters of the protective effects of substance P administration on JP-8-induced immunotoxicity. Finally, we have completed our investigations into the immunotoxicological effects of other jet fuel sources.

The work from this grant has resulted in several manuscripts being published and submitted for publication, as well as the granting of several patent applications (please see below). Our collaboration with Dr. Mark Witten (also at the University of Arizona and also funded by the AFOSR) continues to operate smoothly, maximizing experimental outcomes while minimizing animal use.

The results from this grant has aided us in understanding the actions of substance P on protection of the immune system from the immunotoxicological effects of JP-8 jet fuel exposure, as well as providing us with an insight into the potential effects of JP-8 and other jet fuel sources on clinical disease manifestations.

ACCOMPLISHMENTS/NEW FINDINGS:

During the three years of experimentation we have examined the immunotoxicological effects of JP-8 jet fuel exposure. Inbred C57BL6 mice were exposed to varying concentrations (either 500, 1000 or 2500 mg/m³) of aerosolized JP-8 jet fuel for a period of 7 days with an exposure period of 1 hour per day. Animal exposure was performed via nose-only presentation while the animals were held in individual subject loading tubes. The tubes were nose cone fitted to receiving adapters that originated from a common anodized aluminum exposure chamber. Nose only exposure was utilized to minimize ingestion of jet fuel during self grooming. Animals were rotated on a daily basis through the 12 adapter positions on the exposure chamber. This rotation was done to minimize proximity to the jet fuel source as a variable in exposure concentration or composition. Exposure concentration was determined by a seven stage cascade impactor, and was measured after each exposure. 24 hours after the last exposure the animals were sacrificed and examined for changes in immune system composition and function. The major immune system organ systems (i.e., spleen, thymus, lymph nodes, blood and bone marrow) were recovered and examined for changes in organ weight, total cell numbers, immune cell components (by differential histochemical staining), and lymphocyte subpopulations by flow cytometric analyses. Assays were also performed to assess any changes in immune function in these organs. In some experiments the animals were administered an aerosolized concentration of the neuropeptide substance P (SP, 1 uM) either before or after JP-8 exposure in an effort to protect from or reverse the effects of JP-8 exposure. As controls, other animals were exposed only to air plus/minus SP (i.e., no JP-8 exposure). These studies have resulted in four published manuscripts, three manuscripts submitted for publication, and six abstracts.

The following significant observations were obtained during this period of work on these grant projects. The findings from these studies are summarized as follows.

Manuscript #1 (Harris et al, Immunotoxicological Effects of JP-8 Jet Fuel Exposure, Toxicology & Industrial Health 13(1):43, 1997).

1. JP-8 exposure results in significant depression in immune organ wet weights (spleen and thymus).
2. JP-8 exposure results in significant losses of immune organ cell numbers (spleen, thymus, lymph nodes, peripheral blood and bone marrow).
3. JP-8 exposure causes a significant loss of immune function, as assessed by mitogenic responses, which cannot be overcome by exogenous growth factors.
4. JP-8 exposure has significant effects on the immune system at concentration exposures as low as 100 mg/m^3 (thymus only).
5. The effects of JP-8 on the immune system are concentration-dependent. The majority of the effects of JP-8 exposure on the immune system are observed to begin at concentration exposures between $250\text{-}500 \text{ mg/m}^3$. Concentration exposures of 2500 mg/m^3 are generally thought to be directly toxic to the immune system.
6. No significant differences were observed in immune system effects based on gender of the exposed mice (i.e., male and female animals demonstrated comparable effects).
7. No significant differences were observed in immune system effects using either normal C57Bl/6 mice or enzyme-deficient congenic mice (deficient in two enzymes thought to be involved in hydrocarbon metabolism), indicating that the effects on the immune system were so severe that loss of these putatively important protective enzyme pathways was not relevant.

Manuscript #2 (Harris et al, Short-Term Exposure to JP-8 Jet Fuel Results in Longterm Immunotoxicity, Toxicology & Industrial Health 13(5), 559-570, 1997).

8. Short-term exposures to JP-8 jet fuel results in depressions in wet weights of spleen and thymus which recover within 1 week, although some overcompensation occurs in the thymus.
9. Short-term exposure to JP-8 jet fuel results in significant losses of immune cells from the spleen which takes up to 1 month to recover to normal. Cell losses from the thymus however, recover more quickly.
10. Short-term exposure to JP-8 jet fuel does not appear to have any significant long-term effects on immune cell numbers isolated from lymph nodes, peripheral blood or bone marrow.

11. Short-term exposure to JP-8 jet fuel has significant and long-lasting effects on immune function. The higher the exposure concentration, the longer it takes for the immune system to recover (4 weeks or longer).
12. Immune system effects due to short-term (7 day) exposures are reversible (although not completely) after 3-4 weeks, indicating that even short-term, low concentration exposures have long-lasting effects on the immune system.

Manuscript #3 (Harris et al, Protection from JP-8 Jet Fuel Induced Immunotoxicity by Administration of Aerosolized Substance P, Toxicology & Industrial Health 13(5), 571-588, 1997).

13. The effects of JP-8 exposure on the immune system can be reversed/prevented by administration of substance P (1 uM, 15 minutes) immediately after the jet fuel exposure.
14. Concentrations of substance P as low as 1 nM have significant protective effects against JP-8 induced immune system effects.
15. The effects of JP-8 exposure on the immune system are made worse by administration of substance P inhibitors.

Manuscript #4 (Harris et al, Effects of Short-Term JP-8 Jet Fuel Exposure on Cell-Mediated Immunity, Toxicology & Industrial Health 16:78-84, 2000)

16. JP-8 exposure results in the complete loss of natural killer (NK) cell function, which is long-lasting and results in the inability to give rise to lymphokine-activated killer (LAK) cell activity.
17. JP-8 exposure results in the complete loss of cytotoxic T lymphocyte (CTL) function.
18. JP-8 exposure results in the significant suppression of the ability of precursor T cells to give rise to lymphokine producing T cells (i.e., helper T cells).
19. JP-8 exposure results in the significant suppression of the ability of precursor T cells to give rise to cytotoxic T cells (i.e., CTL).

Manuscript #5, accepted for publication (Harris et al, Jet Fuel-Induced Immunotoxicity; Toxicology & Industrial Health)

20. Exposure of mice to JP-8+100 jet fuel is just as detrimental as exposure to standard JP-8 jet fuel in terms of its effects on the immune system.

21. Exposure of mice to Jet A-1 jet fuel is just as detrimental as exposure to standard JP-8 jet fuel in terms of its effects on the immune system.

Manuscript #6, accepted for publication (Harris et al, Substance P as Prophylaxis for JP-8-Induced Immunotoxicity; Toxicology & Industrial Health)

22. Exposure of mice to aerosolized substance P 15 minutes prior to JP-8 jet fuel exposure protects the immune system from the detrimental effects of JP-8 jet fuel exposure, as does administration 15 minutes post-exposure. However, a 1 or 6 hour pre-exposure treatment is not effective.
23. Exposure of mice to aerosolized substance P 1 or 6 hours post-exposure to JP-8 is almost as effective as exposure to substance P 15 minutes post-JP-8 exposure.

Manuscript #7, submitted for publication (Harris et al, JP-8 Jet Fuel Immunotoxicity Occurs Rapidly and is Cumulative; Toxicology & Industrial Health)

24. Exposure of mice to JP-8 for 1 hour/day initiates a cascade of cumulative effects on the immune system, with toxicological results evident as soon as 1 hour post-exposure.
25. There is a cumulative loss of spleen (maximal by day 5) and thymus (maximal by day 4) organ weights due to JP-8 exposure.
26. There is a cumulative loss of immune function due to JP-8 exposure, which is maximal by day 4 of exposure.

Manuscript #8, submitted for publication (Harris et al, JP-8 Exposure Rapidly Induces High Levels of IL-10 Secretion and Is Correlated With Loss of Immune Function; Toxicology & Industrial Health)

27. JP-8 exposure rapidly induces a persistently high level of serum IL-10 at exposure concentrations from 500-2500 mg/m³.

28. IL 10 levels peak at 2h post-JP-8 exposure and then stabilize at significantly elevated serum levels.

29. Elevated IL 10 levels may at least partially explain the effects of JP-8 exposure on immune function.

30. Elevated IL 10 levels however, cannot explain all of the effects due to JP-8 exposure (e.g., decreased organ weights and decreased viable immune cells).

From the experiments that have been performed to date it appears that the immune system is a sensitive indicator of toxicological damage incurred by the individual due to JP-8 jet fuel exposure, as well as exposure to other sources of jet fuel. The results summarized above have indicated that exposure to JP-8 (and other sources of) jet fuel, even at low concentrations and even for short periods of time, has significant and profound effects on the immune system. JP-8 should be considered a significant immunotoxicant. It would be expected that such immune system changes in immunocompetence that have been observed after JP-8 exposure would have significant effects on the exposed individual's health and may adversely affect his/her susceptibility to infectious disease, as well as possibly the development and/or progression of cancer.

OVERALL CONCLUSIONS

Short-Term Effects of JP-8 Exposure

1. A single 1h, 1000 mg/m³ JP-8 exposure results in immediate immune effects detectable within hours after jet fuel exposure.
2. Significant weight loss is observed in the spleen at 1h post-exposure and in the thymus at 4h post-exposure.
3. Immediate effects on the recovery (i.e., loss) of viable immune cells are observed.
 - A. Spleen : occurs by 1h, which does not recover by 24h.
 - B. Thymus : occurs by 1h, which recovers to 85% by 24h
 - C. Bone Marrow : occurs by 1h, which overcompensates and recovers to 100% by 24h.
 - D. Blood : occurs by 1h, exhibits greatest decrease but recovers to 80% by 24h.
4. There is an immediate loss of immune function that does not change or recover over the next 24h post-exposure.

Cumulative Effects of JP-8 Exposure

1. A 1h/day, 1000 mg/m³ JP-8 exposure results in cumulative immune effects detectable over the next several days after jet fuel exposure.
2. There is a cumulative loss of spleen (maximal by day 5) and thymus (maximal by day 4) organ weights due to JP-8 exposure.
3. There is a cumulative loss of viable immune cells due to JP-8 exposure.
 - A. Spleen : maximal by day 4
 - B. Thymus : maximal by day 5
 - C. Bone Marrow : maximal by day 6-7
 - D. Blood : maximal by day 6-7

4. There is a cumulative loss of immune function due to JP-8 exposure, which is maximal by day 4 of exposure.

PERSONNEL SUPPORTED:

David T. Harris, Ph.D.	Principle Investigator
Thomas Tsang, Ph.D.	Senior Research Scientist
Farha Vasanwala, BS	Doctoral Graduate Student (has now graduated)
Debbie Sakiestewa, BS	Senior Research Technician
Dominic Titone	Howard Hughes Honors Undergraduate Student (has now graduated)

PUBLICATIONS:

The following publications either have been published or have been submitted for publication. Abstracts from scientific conferences that have been published are also available upon request.

Harris et al, Immunotoxicological Effects of JP-8 Jet Fuel Exposure, Toxicology & Industrial Health 13(1):43, 1997.

Harris et al, Short-Term Exposure to JP-8 Jet Fuel Results in Longterm Immunotoxicity, Toxicology & Industrial Health 13(5), 559-570, 1997.

Harris et al, Protection from JP-8 Jet Fuel Induced Immunotoxicity by Administration of Aerosolized Substance P, Toxicology & Industrial Health 13(5), 571-588, 1997.

Harris et al, Effects of Short-Term JP-8 Jet Fuel Exposure on Cell-Mediated Immunity, Toxicology & Industrial Health 16:78-84, 2000.

Harris et al, Jet Fuel-Induced Immunotoxicity, Toxicology & Industrial Health, accepted for publication, 2000.

Harris et al, Substance P as Prophylaxis for JP-8-Induced Immunotoxicity, Toxicology & Industrial Health, accepted for publication, 2000.

Harris et al, JP-8 Jet Fuel Immunotoxicity Occurs Rapidly and is Cumulative; Toxicology & Industrial Health, submitted for publication.

Harris et al, JP-8 Exposure Rapidly Induces High Levels of IL-10 Secretion and Is Correlated With Loss of Immune Function; Toxicology & Industrial Health, submitted for publication.

INTERACTIONS/TRANSITIONS:

1. Meetings, Conferences, Seminars

AFOSR Toxicology Conference in Dayton, OH, December 1997
AFOSR JP-8 Meeting at The University of Arizona, Tucson, AZ; May 1998
AFOSR Toxicology Conference in San Antonio, TX; April 1998
AFOSR JP-8 Meeting at The University of Arizona, Tucson, AZ, December 1998.
AFOSR JP-8 Jet Fuel Toxicology Workshop, Tucson, AZ, 11-12 January 2000

2. Consultants

Cord Blood Registry, Inc.
NanoTek, Inc.
Medical Advisory Board, Canadian J. Clin. Med-Medical Scope Monthly
Chief Immunologist and Director, Odyssey Corporation
Teltech, Inc.
Ageria Corporation

3. Transitions

None to date. However, the Air Force has shown considerable interest (i.e., Wright Patterson Labs) with regard to the potential effects of JP-8 exposure on human personnel, as well as the actions of substance P in protecting from any immunotoxicological effects.

PATENTS/INVENTIONS:

The following patents originated from work performed on our Air Force Office of Scientific Research sponsored grant entitled, "Immunotoxicology of Exposure to JP-8 Jet Fuel". The patents, as well as our grant work, have been performed in conjunction with Dr. Mark Witten (Dept. of Pediatrics, University of Arizona). Because of the laws involving public disclosure during the patent process, we have been slightly delayed in some of our publications related to substance P. However, as we are now in discussions with several pharmaceutical companies regarding this discovery, this issue should be shortly resolved. This discovery may have significant clinical benefits in terms of boosting the immune systems of individuals that are immunocompromised (e.g., AIDS patients, cancer patients, aged individuals, etc.), as well as been of benefit to those exposed to environmental toxicants (e.g., hydrocarbons, cigarette smoke, etc.). Further, we are now in discussions with another pharmaceutical company with regard to licensing for effects on cognitive functions.

Substance P Treatment for Immunostimulation-Cancer Therapy, 1999, #5,945,508

Substance P Treatment for Immunostimulation-Immunomodulation, 1999, #5,998,376

HONORS/AWARDS:

1999-2000	Elected to "Who's Who in Medicine and Healthcare"
1999	Elected to "Who's Who in America"
1999	Elected to "Who's Who in the West"
2000-2001	Elected to "Who's Who in the West"
2000	Elected to "Who's Who in America"
2000	Elected to "Who's Who in the World"
2000-2001	Elected to "Who's Who in Medicine and Healthcare"
2001	Elected to "Who's Who in America"

BIOGRAPHY : DAVID T. HARRIS, PH.D.

Dr. Harris is a graduate of Wake Forest University in Winston-Salem, North Carolina where he obtained Bachelor of Science degrees (cum laude) in Biology, Mathematics and Psychology in 1978. He earned a Masters of Medical Sciences (summa cum laude) from Bowman Gray Medical School in 1980 and his Doctorate in Microbiology and Immunology (magna cum laude) from Bowman Gray Medical School in 1982. From 1982-1985 Dr. Harris was a Postdoctorate Fellow at the Ludwig Institute for Cancer Research in Lausanne, Switzerland. In 1985 he joined the faculty at the University of North Carolina-Chapel Hill as a Research Assistant Professor in the Department of Medicine where upon he began his work in immunotoxicology via collaborations with the EPA. In 1989 Dr. Harris joined the faculty at the University of Arizona in Tucson as an Associate Professor in the Department of Microbiology & Immunology. In 1996 Dr. Harris was promoted to Professor of Immunology. He currently also serves as Director of the Cord Blood Stem Cell Bank, is a member of the Arizona Cancer Center, a member of the Children's Research Center, a member of the Arizona Arthritis Center, and Head of the Gene Therapy Group. Dr. Harris's research interests include immunotoxicology, cancer research, transplantation and gene therapy. He has published more than 200 articles and has served as a consultant to the governments of China, Hong Kong, Singapore and South Korea. Dr. Harris has worked with the AFOSR on the immunotoxicity of JP-8 jet fuel since 1994.